Does excluding subjects with features similar to IPF affect the results of the INBUILD® trial of nintedanib?

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Introduction

- The INBUILD trial enrolled subjects with chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype except for idiopathic pulmonary fibrosis (IPF), for which approved treatments were already available.
- Compared with placebo, nintedanib reduced the rate of decline in forced vital capacity (FVC) (mL/year) over 52 weeks by 57% in the overall population and by 61% in subjects with a usual interstitial pneumonia (UIP)-like fibrotic pattern on HRCT (co-primary analysis populations).[1]
- In the differential diagnosis of ILDs, it can be challenging to separate idiopathic from nonidiopathic disease[2] and to differentiate the idiopathic interstitial pneumonias (IIPs)[3], and some ILDs remain unclassifiable even after multidisciplinary review.[4]

Aim

- To investigate the effect of excluding subjects with features similar to IPF on the results of the INBUILD trial.

Methods

Trial design[1]

- Subjects in the INBUILD trial had an ILD other than IPF, diagnosed according to the investigator's usual clinical practice. Diagnoses were grouped into hypersensitivity pneumonitis, autoimmune ILDs, idiopathic non-specific interstitial pneumonia (iNSIP), unclassifiable IIP, other ILDs.[5]
- Measures were implemented to ensure that patients with IPF were excluded:

Diagnosis of IPF based on ATS/ERS/JRS/ALAT 2011 guidelines[6] was an exclusion criterion.

The importance of excluding patients with IPF was emphasised to investigators and specific training was provided.

If central review of HRCT identified a UIP-like fibrotic pattern[7], the investigator had to confirm that the subject did not have IPF.

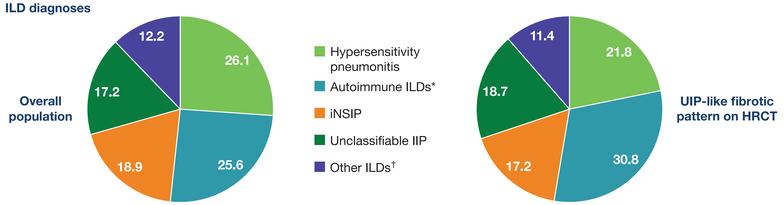
- Subjects had reticular abnormality with traction bronchiectasis (with or without honeycombing) of >10% extent on HRCT, FVC ≥45% predicted, diffusing capacity for carbon monoxide (DLco) ≥30%–<80% predicted, and met criteria for ILD progression in the 24 months before screening, despite management deemed appropriate in clinical practice.
- Subjects were randomised to receive nintedanib or placebo, stratified by fibrotic pattern on HRCT (UIP-like fibrotic pattern or other fibrotic patterns).

Analyses

- We assessed the effect of nintedanib vs placebo on the rate of decline in FVC (mL/year) over 52 weeks:
  - excluding subjects in the five diagnostic groups one by one
  - excluding subjects with unclassifiable IIP or iNSIP with a UIP-like fibrotic pattern on HRCT
  - excluding subjects with clinical characteristics typical of IPF (male, age >65 years, current or former smoker, UIP-like fibrotic pattern on HRCT).
- Analyses were performed in the overall population and in subjects with a UIP-like fibrotic pattern on HRCT.

Results

ILD diagnoses



*Included rheumatoid arthritis-associated ILD, systemic sclerosis-associated ILD, mixed connective tissue disease-ILD, plus subjects with an autoimmune disease noted in the "Other fibrosing ILDs" category of the case report form. †Included sarcoidosis, exposure-related ILDs and selected terms in the "Other fibrosing ILDs" category of the case report form.

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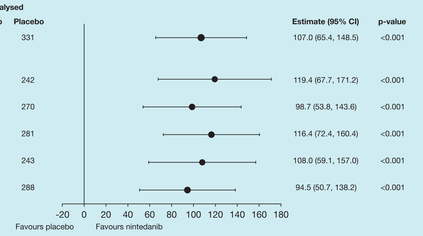
Analyses excluding diagnostic groups one by one[5]

- Analyses in which the five diagnostic groups were excluded one by one suggested that no diagnostic group drove the treatment effect in the overall population or in subjects with a UIP-like fibrotic pattern on HRCT.

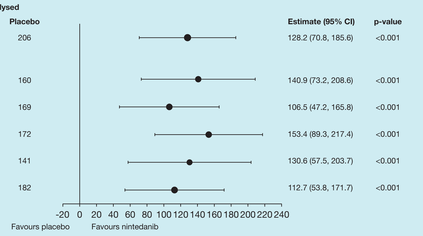
Overall population

	n analysed		Estimate (95% CI)	p-value
	Nintedanib	Placebo		
All patients	332	331	107.0 (65.4, 148.5)	<0.001
iNSIP, unclassifiable IIP, autoimmune ILDs, other fibrosing ILDs **(excludes HP)**	248	242	119.4 (67.7, 171.2)	<0.001
HP, unclassifiable IIP, autoimmune ILDs, other fibrosing ILDs **(excludes iNSIP)**	267	270	98.7 (53.8, 143.6)	<0.001
HP, iNSIP, autoimmune ILDs, other fibrosing ILDs **(excludes unclassifiable IIP)**	267	281	116.4 (72.4, 160.4)	<0.001
HP, iNSIP, unclassifiable IIP, other fibrosing ILDs **(excludes autoimmune ILDs)**	250	243	108.0 (59.1, 157.0)	<0.001
HP, iNSIP, unclassifiable IIP, autoimmune ILDs **(excludes other ILDs)**	293	288	94.5 (50.7, 138.2)	<0.001



UIP-like fibrotic pattern on HRCT

	n analysed		Estimate (95% CI)	p-value
	Nintedanib	Placebo		
All patients	206	206	128.2 (70.8, 185.6)	<0.001
iNSIP, unclassifiable IIP, autoimmune ILDs, other fibrosing ILDs **(excludes HP)**	162	160	140.9 (73.2, 208.6)	<0.001
HP, unclassifiable IIP, autoimmune ILDs, other fibrosing ILDs **(excludes iNSIP)**	172	169	106.5 (47.2, 165.8)	<0.001
HP, iNSIP, autoimmune ILDs, other fibrosing ILDs **(excludes unclassifiable IIP)**	163	172	153.4 (89.3, 217.4)	<0.001
HP, iNSIP, unclassifiable IIP, other fibrosing ILDs **(excludes autoimmune ILDs)**	144	141	130.6 (57.5, 203.7)	<0.001
HP, iNSIP, unclassifiable IIP, autoimmune ILDs **(excludes other ILDs)**	183	182	112.7 (53.8, 171.7)	<0.001



Analyses excluding subjects with unclassifiable UIP or iNSIP plus a UIP-like fibrotic pattern on HRCT

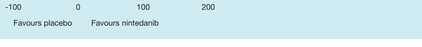
- When subjects with unclassifiable IIP or iNSIP and a UIP-like fibrotic pattern on HRCT were excluded from the analyses, the effect of nintedanib vs placebo on reducing the rate of decline in FVC over 52 weeks (mL/year) was similar to the primary analyses.

Overall population

	n analysed		Nintedanib vs placebo difference in adjusted annual rate of decline in FVC (95% CI)	p-value
	Nintedanib	Placebo		
All subjects	332	331	107.0 (65.4, 148.5)	<0.0001
Excluding subjects with unclassifiable IIP or iNSIP with UIP-like fibrotic pattern on HRCT	255	260	102.8 (58.5, 147.2)	<0.0001

UIP-like fibrotic pattern on HRCT

	n analysed		Nintedanib vs placebo difference in adjusted annual rate of decline in FVC (95% CI)	p-value
	Nintedanib	Placebo		
All subjects	206	206	128.2 (70.8, 185.6)	<0.0001
Excluding subjects with unclassifiable IIP or iNSIP with UIP-like fibrotic pattern on HRCT	129	135	131.7 (65.1, 198.4)	0.0001

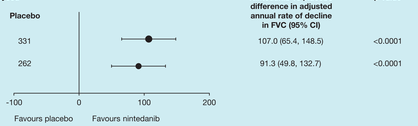


Analyses excluding subjects with clinical characteristics typical of IPF

- When subjects with clinical characteristics typical of IPF were excluded from the analyses, the effect of nintedanib vs placebo on reducing the rate of decline in FVC over 52 weeks (mL/year) was similar to the primary analyses.

Overall population

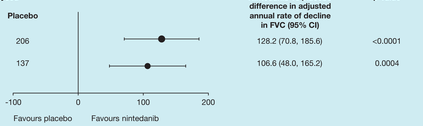
	n analysed		Nintedanib vs placebo difference in adjusted annual rate of decline in FVC (95% CI)	p-value
	Nintedanib	Placebo		
All subjects	332	331	107.0 (65.4, 148.5)	<0.0001
Excluding subjects with clinical characteristics typical of IPF*	270	262	91.3 (49.8, 132.7)	<0.0001



*Male, age >65 years, current or former smoker, UIP-like fibrotic pattern on HRCT.

UIP-like fibrotic pattern on HRCT

	n analysed		Nintedanib vs placebo difference in adjusted annual rate of decline in FVC (95% CI)	p-value
	Nintedanib	Placebo		
All subjects	206	206	128.2 (70.8, 185.6)	<0.0001
Excluding subjects with clinical characteristics typical of IPF*	144	137	106.6 (48.0, 165.2)	0.0004



*Male, age >65 years, current or former smoker, UIP-like fibrotic pattern on HRCT.

Conclusion

- **In the INBUILD trial, excluding subjects for whom making a differential diagnosis versus IPF is most challenging did not have a relevant impact on the effect of nintedanib on reducing the rate of decline in FVC in subjects with chronic fibrosing ILDs and a progressive phenotype. These findings suggest that the treatment effect of nintedanib observed in the INBUILD trial was not the result of patients with misdiagnosed IPF being included in the trial.**

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